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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,586	03/01/2004	David G. Bermudes	872-A-US	9589

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EXAMINER	
VOGEL, NANCY S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,586	BERMUDES ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 and 11-18 are pending in the case. Receipt of the preliminary amendment of 3/1/04 is acknowledged.

Information Disclosure Statement

Applicant is notified that the citation number 1 (which is the application number of the parent application of the instant application) listed on the information disclosure statement submitted 3/1/04, has been considered, but has been crossed through, since the printing of an patent application number on the face of any issued patent would not be appropriate. The references listed on the copy of the "Notice of References Cited" form, originally present in parent application 10/076,117, have been considered.

Specification

The disclosure is objected to because of the following informalities: page numbers on the Table of Contents pages of the specification (i-ii) do not correspond to the page numbering of the rest of the specification.

Appropriate correction is required.

Claim Objections

The Markush group language should be perfected in claims 6. It would be remedial to amend the claims to read "the group consisting of a".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 11-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 1 covers a pharmaceutical composition comprising an attenuated, tumor-targeting Gram-negative bacterium containing a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of an eukaryotic promoter or as part of a fusion with a capsid protein. Claim 8 covers a kit comprising the pharmaceutical composition of claims 1. Claim 9 covers a kit comprising the pharmaceutical composition of claim 1

wherein the bacterium is expressing the F' pilus. Claim 11 covers a method for delivering an agent comprising administering the composition of claim 1. Claim 14 covers a method for delivering an agent comprising the administering the composition of claim 1 wherein the bacterium is expressing the F'pilus. Claim 15 covers a method of inhibiting tumor growth or reducing tumor volume comprising administering a tumor-targeting bacterium containing a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of an eukaryotic promoter or as part of a fusion with a capsid protein. Claim 17 covers a method of inhibiting tumor growth or reducing tumor volume comprising administering a tumor-targeting bacterium expressing the F' pilus and a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of a n eukaryotic promoter or as part of a fusion with a capsid protein. The bacterium may be any Gram-negative bacterium, the gene product of interest can be virtually anything, the composition can be administered by any route, and the method can be used for treatment of any tumor-based disease.

The nature of the invention is a pharmaceutical composition comprising an attenuated, tumor-targeting Gram-negative bacterium containing a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of an eukaryotic promoter or as part of a fusion with a capsid protein, kits comprising the pharmaceutical composition, and methods for delivering an agent and methods of inhibiting tumor growth or reducing tumor volume, wherein the methods comprise administering either a composition comprising a tumor-targeted bacterium containing a recombinant bacteriophage, or a composition comprising a tumor-targeted bacterium

expressing the F' pilus and a recombinant bacteriophage encoding a gene of interest. The only disclosed use for the pharmaceutical composition is gene therapy treatment and the claims have been examined in light of this. The delivery of a nucleic acid in vivo or ex vivo for therapeutic purposes constitutes gene therapy. Thus, the claimed methods represent methods for gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows a complete lack of documented success for gene therapy. In a review on the current status of gene therapy, Mitchell ((1998) Lancet 351:346) quotes Inder Verma, a leading authority on gene therapy: "No form of gene therapy can yet be considered a success, and the major problem still lies in delivery mechanisms". Bacteria as a delivery mechanism are described as "exotic non-viral vectors". Additionally, "little is known as yet about whether these approaches will work and at the moment non-viral vectors are too inefficient to treat genetic and most acquired diseases" (attributed to Verma). Generally, although there is promise for progress in gene therapy, it still remains the case that "all gene-transfer methods tend to be more efficient in vitro than in vivo...so many tumour cells in the body may be left unmodified and resistant to [gene-directed enzyme prodrug therapy]" (Bonn (1999) Lancet 354:1364).

Regarding the use of bacteria as DNA delivery systems to mammalian cells, in order for such systems for be successful, the bacteria must first enter the cell and then escape from the vacuole to the cytosol. Movement from the vacuole to the cytosol is unpredictable because in many instances the bacteria are lysed by the host cell's

defense system and any plasmids carried by the bacterial are degraded preventing expression of heterologous nucleotide sequences. At best it would appear that only a few cells, if any, may be transformed with DNA carried by a bacterial vehicle as Grillot-Courvalin (Nature Biotechnology, 1998, 16:862-866) suggest that "direct introduction of DNA from bacteria to mammalian cells has been reported in very few instances" (page 865, discussion). Grillot-Courvalin support such observations by reporting that "factors such as entry route may have an effect" on DNA delivery. Grillot-Courvalin go on to report that a mouse dendritic cell line, which can internalize bacteria via micropinocytosis, did not express incoming DNA at 24 hours post-transfer. Grillot-Courvalin suggest that this failure could reflect rapid degradation of the invading bacteria by this cell type. It would appear that use of bacteria as DNA delivery vehicles is not very efficient in other cell lines as well as Grillot-Couvalin have reported that *E. coli* carrying a nucleotide sequence encoding the green fluorescent protein are only able to transform 0.3-1% of a transfected macrophage cell line. (see paragraph bridging pages 864-865). These observations are corroborated by Dietrich et al. (Nature Biotechnology, 1998, 16:181-185) who report that only about 0.03% of macrophages infected with a mutated form of *Listeria monocytogenes* express a green fluorescent protein reporter gene (page 183, column 2). Dietrich et al. also suggest that expression of a heterologous nucleotide sequence is not stable over time by observing a gradual loss of fluorescence over time. See page 183 at bottom of column 2. Dietrich report that the low efficiency of expression of GFP as compared to the number of macrophages infected may be due to the fact that only some of the attenuated bacteria

infecting the host cells survive the antimicrobial milieu inside the phagosome and are able to escape into the host cell cytosol, whereas the others are totally digested, including the plasmid DNA, and that not all *Listeriae* being taken up reach the host cell cytosol as an intact viable entity, but the plasmid DNA is still released into this compartment (see page 184 at top of column 2). Therefore, there is ample evidence in the prior art that the delivery of heterologous genes to eukaryotic cells via bacterial vectors is unpredictable and far from routine.

Regarding the route of administration, the claimed invention encompasses delivery by administering the bacteria by any route, however, it is not routine in the art to administer the bacteria by any route. While the art teaches administration of attenuated bacteria by the oral route, the issues of unpredictability regarding antigen stability and antigen expression at a level sufficient to induce an immune response abound. A general issue of unpredictability of oral vaccines is the poor immunogenicity displayed by most antigens when given orally. See Pascual et al (Behring Inst. Mitt., 1997, 98: 143-152) on page 143. Pascual et al. report that there are several issues compounding the development of live oral bacterial vaccine vectors, including the fact that there is a "lack of a well tolerated, highly immunogenic bacterial vector for use in humans" (page 144). While the instantly claimed invention is not directed to vaccination and is directed to tumor directed delivery, the issues of unpredictability discussed above will be applicable in the instant case.

Therefore, the state of the art as evidenced above suggests that use of bacteria as a vehicle for transferring heterologous nucleotide sequences to eukaryotic cells of an

animal is undeveloped, inefficient, and unpredictable. The studies recited above demonstrate that only low efficiency of reporter gene expression occurs in cell line in vitro and only contemplate that bacteria could be used to transfer heterologous DNA sequences to the cells of an organism.

The relative skill of those in the art of recombinant DNA techniques and microbiology is high. The relative skill of those in the art of gene therapy and treatment of solid tumors using gene therapy is low.

The area of the invention is unpredictable. As discussed above, the method of gene therapy in general, and the use of bacteria as delivery systems to eukaryotic cells in vivo in particular, is highly complex and unpredictable and the skilled artisan at the time of the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Thus, the effectiveness of a potential new delivery system, such as tumor-targeted bacteria containing a bacteriophage encoding a gene of interest, cannot be predicted in the absence of in vivo testing for a therapeutic effect.

The present specification provides little direction or guidance to support the claimed invention. The specification generally discloses a wide variety of possible genes of interest to be encoded by the bacteriophage, multiple routes of administration are taught, and numerous solid tumor cancers are suggested targets of the therapy. No direction is provided on how to generate tumor target bacterium in Gram-negative species other than Salmonella; indeed the basis for the tumor targeting in the Salmonella used is not disclosed; thus it is unclear if one could readily generate such

tumor targeting in other Salmonella strains or serotypes, unless it is an inherent property of all Salmonella. Furthermore, no direction as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. the inefficiency of non-viral vectors, especially the inefficiency in in vivo usage, is provided.

No working examples are disclosed in which the method of inhibiting tumor growth or reducing tumor volume using a composition comprising a tumor-targeted bacteria is used to treat a solid tumor cancer and tumor growth is inhibited or tumor volume is reduced. An example is disclosed wherein Salmonella expressing F'pilus are infected with a phagemid in which the gene of interest is green fluorescent protein (GFP) and are used to infect mammalian M2 cells. Expression of GFP is shown. Another example discloses injecting mice containing melanoma tumors with Salmonella that are expressing F' pilus and are infected with filamentous phage M13KO7. Tumor and liver homogenates and supernatants are compared for the presence of bacteria and the presence of phage. No demonstration of gene expression or therapeutic effect due to expression of a gene of interest is made in this example. Furthermore, it is highly questionable whether a mouse model provides a basis for predictability of results in higher order mammals, specifically humans. See Gura (Science, Vol. 278, pp. 1041-1042, 1997).

The quantity of experimentation necessary to carry out the claimed invention is high since the skilled artisan could not rely on the prior art of the present specification to teach how to use the claimed method. In order to demonstrate how to use the method to inhibit tumor growth or reduce tumor volume of any solid tumor

cancer, one of skill in the art would have to determine if a gene of interest encoded by a bacteriophage and delivered by a bacteria is delivered efficiently and preferentially to the targeted tumor type, if the gene of interest is expressed efficiently, and if such expression provides any therapeutic effect. Furthermore, given the broad range of possible methods of administration, one must determine if the bacterial composition would survive and bacteria would reach the targeted tumors efficiently and in sufficient number to achieve a therapeutic effect, rather than being targeted by the immune system to some degree, despite their attenuated pathogenicity. Since neither the prior art nor the specification provides the answers to all of these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method comprising administering either a composition comprising a tumor-targeted bacterium containing a recombinant bacteriophage, or a composition comprising a tumor targeted bacterium expressing the F' pilus and a recombinant bacteriophage encoding a gene of interest to inhibit tumor growth or reduce tumor volume.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 11-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 9, 11, 14, 15, 17, and by dependence claims 2-7, 12, 13, 16 and 18, are vague and indefinite in the recitation of the phrase "the genome of the bacteriophage has been modified to encode the gene of interest as a fusion protein", since a gene cannot be "encoded" as "a fusion protein", and therefore the intended metes and bounds of the invention cannot be determined. The claim has been examined as if it recited that the genome is modified to comprise a gene of interest fused with a gene encoding a bacteriophage capsid protein.

Claims 3-5, 12 and 13 are vague and indefinite in the recitation of "[t]he composition according to claim 1 in which the gene product of interest is ..." (claims 3-5) and "[t]he method according to claim 11, in which the gene of interest is..." (claims 12 and 13), since it is not clear whether the "gene of interest" refers to the recited "gene product of interest" in line 6 of claim 11, in addition to the recited "gene of interest" in the line 9 of claim 11 (see above paragraph regarding the indefiniteness of the phrase "gene product of interest" in line 6 of claim 11).

In claim 7, it is unclear whether the limitation is intended to change the Markush group to be: "a cytokine, a bacteriocin, a pro-drug converting enzyme and an anti-angiogenic agent" or if the limitation is a composition in which the molecule is a

cytotoxin which is specifically a bacteriocin. Thus, the metes and bounds of the claim cannot be determined.

Claims 11 and 14, and by dependence, claims 12 and 13, are vague and indefinite in the recitation of the term "agent", since it is not clear what is meant by this term, and what this term encompasses is not expressly defined in the specification. Therefore, the metes and bounds of the intended subject matter cannot be determined.

Claim 12 is vague and indefinite in the recitation of "the gene of interest is an antigen or a pro-drug converting enzyme" (claim 12), since it is not clear how a gene can be a pro-drug converting enzyme. Enzymes are generally known to be proteins, rather than genes, and the specification does not describe any "genes of interest" which act as antigens or enzymes. Presumably, it is intended that the recited "gene of interest" encodes the antigen or pro-drug converting enzyme, and the claim has been examined as if this were recited.

Claim 13 is vague and indefinite in the recitation of "the gene of interest is fused with a bacteriophage capsid protein", since this is apparently not what is intended when read in light of the specification. Presumably, the "gene of interest" is fused to a gene encoding a "bacteriophage capsid protein", and the claim has been examined as if this were recited.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:30 - 4:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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